THE ASSESSMENT OF RISKS FROM OCCUPATIONAL
EXPOSURE TO IONIZING RADIATION

by

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The Assessment of Risks from Occupational Exposure to
to Ionizing Radiation

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Abstract. The assessment of health effects from occupational exposure to radiation presents a variety of problems resulting from the time dependent nature of the exposure data, the more favorable health frequently experienced by working populations, and limits imposed by the size of the populations and the magnitudes of the exposures received. A proportional hazards model is used to derive tests for determining if statistically significant effects are present and is also considered for point estimation. Because effects of the size expected from current estimates are unlikely to be detected in occupationally exposed groups, methods of calculating upper confidence limits are considered. Data from the Hanford plant are used to illustrate many of the problems and procedures.

1. Introduction. The evaluation of health effects in populations occupationally exposed to radiation is a matter of considerable current controversy. Existing standards for occupational exposure are based primarily on estimates of health effects obtained by linear extrapolation from effects at high level exposures, such as those experienced at Hiroshima and Nagasaki or by British patients treated with irradiation for ankylosing spondylitis. It would obviously be desirable to assess the adequacy of these estimates directly in populations of workers actually receiving the exposures. It must, however, be recognized that the amount that can be learned from such populations is limited by the size of the populations and the magnitude of the exposures received. Nevertheless, it is important that such groups be

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studied primarily to evaluate the hypothesis that effects might be many times larger than indirect estimates would suggest.

It is the aim of this presentation to discuss methods of analyzing occupational radiation exposure data with emphasis on data from the Hanford plant. This plant, which has employed many workers in jobs involving some exposure to radiation, was established in the early forties as an installation for plutonium production. Annual records of radiation exposure have been obtained from dosimeters worn by employees. These data consist of estimates of exposure to several types of ionizing radiation, but only radiation that is able to reach the internal organs (whole body penetrating radiation) is considered here. Such exposure is measured in rem, a normalized sum of several radiation types.*

Health effects data are limited to mortality. Life status is established by a Social Security Administration search of their files. Death certificates are obtained from the states where deaths occurred, and the cause of death is coded according to the Eighth Revision of the International Classification of Diseases (ICD) [9]. Additional detail on the Hanford data is given in [13].

The potential of the Hanford data can be examined by considering the total amount of radiation received and the effects that would be expected if current estimates are correct. Such estimates are summarized in the BEIR report [8, p. 171] and can be expressed as deaths/ 10^6 /rem/year. Such an expression is based on a linear nonthreshold model and requires the implicit assumptions that effects do not depend on spontaneous risk (absolute model), on dose rate, or on length of time that has elapsed since exposure (for some specified interval). The estimates considered are 1 death/ 10^6 /rem/year for leukemia and 3.5 deaths/ 10^6 /rem/year for

*A rem (Roentgen Equivalent Man) is numerically equivalent to the absorbed dose in rad multiplied by a quality factor expressing the relative biological effectiveness (RBE) of the radiation type. For the Hanford exposures these factors are taken to be 10 for fast neutrons, 3 for slow neutrons, 1.7 for tritium, and 1 for all other types.

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all other cancers. It is assumed that the estimates are valid for any interval two or more years after exposure.

The study population consists of 12,679 monitored white males employed at Hanford for at least two years with initial employment date prior to 1965. If the above estimates are correct, about 0.5 radiation induced deaths from leukemia and 1.7 deaths due to other cancers would be expected by the endpoint of the study, March 31, 1974, resulting from about 53,000 man-rem of exposure. Since 487.7 "spontaneous" cancer deaths (21.6 for leukemia) would be expected in this population based on U.S. mortality rates, it is unlikely that such a small number of radiation induced deaths will be statistically detectable. Furthermore, since linear extrapolation is generally thought to be conservative, and since evidence from animal experiments suggests that effects at low dose rates may be of lesser magnitude than effects at high dose rates [21], the above estimates would be regarded by many as the maximum expected effects. Finally, the assumption that the BEIR report estimates are valid for any period two or more years after exposure may not be realistic for many cancer types.

There is not, however, complete agreement on the conservatism of the above estimates. Recently, considerable publicity has been given to various claims that cancer risks from low level radiation exposure are far higher than previously predicted [4,14] (one such claim is based on an analysis of the Hanford data). Thus, it is important to analyze these data not only from the standpoint of determining whether statistically significant effects are present (which would probably imply a departure from current estimates) but also from the standpoint of checking the consistency of these data with claims that effects may be much larger than current estimates.

2. Exposure data. Before considering methods of analysis, it is relevant to examine certain features of the exposure data. The distribution of cumulative doses through 1973, which is presented in Figure 1,

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Figure 1. Distribution of cumulative doses for white male workers employed at least two years.

is highly skewed, reflecting the fact that the predominant exposure of most Hanford employees is to natural background radiation (typically about 0.1 rem per year). A much smaller number (less than 15% of the work force) receive annual doses in excess of 1 rem with a very small number of those exceeding 4 rem per year (less than 1% of the work force).

Radiation exposure is correlated with a number of variables that may also affect mortality. Calendar year, in particular, is very highly correlated with exposure, partly because of the cumulative nature of exposure but also because annual exposures have increased substantially. For example, the number of annual exposures exceeding 1 rem increased from 30 (0.5% of the work force) in 1950 to 1,730 (20.0% of the work force) in 1965. The increase is probably due to the aging of the plant with accumulation of radioactive materials and more frequent need for

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repairs [10]. The strong correlation of exposure and calendar year is particularly important in evaluating death rates from causes that have increased or decreased with time, lung cancer being the most noteworthy example.

The Hanford mortality study includes the experience of workers not only while they are employed at Hanford but also after termination of employment. (Exposure data, however, is available only during the period of employment.) Because of the strong correlation of exposure with calendar time, a worker who terminates relatively early has little potential for radiation exposure. This is demonstrated in Figure 2, in which average cumulative doses for terminated and employed workers are presented by calendar year. It is well known that working populations

Figure 2. Average accumulated exposure^(a) for workers while employed and after termination of employment by calendar year for white males employed at Hanford at least two years.

(a) This includes exposure accumulated up to two years prior to the specified calendar year. Only exposure of workers surviving until the given calendar year is included.

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tend to have lower death rates than the general population [12]. This "healthy worker effect" can be expected to be greater during actual employment than after termination.

Occupation, which was coded according to categories employed by the Bureau of Census [1], is related to exposure in that most of the higher exposures were received by workers classified as craftsmen or operators (see Figure 3). A more detailed look at these workers indicates that a few specific occupations within this group have high potential for exposure while others have little potential for such exposure. Craftsmen and operators may have smoking habits* and/or occupational exposures which differ from those of the remainder of the Hanford population. It has been demonstrated in other studies that occupation and its associated socioeconomic status affect mortality patterns [16,18].

*Adequate smoking histories are not available.

Figure 3. Average accumulated exposure^(a) for craftsmen and operators and all other workers by calendar year for white males employed at least two years.

See (a) Figure 2.

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Other variables of some importance in this data set include age, length of employment and initial employment date. Age is remarkably uncorrelated with radiation exposure, but certainly must be considered in any mortality analysis. Length of employment has a distinct effect on mortality rates in comparing workers employed for less than two years with those employed at least two years. However, beyond two years the employment period does not show a relationship to mortality patterns. For obvious reasons length of employment is highly correlated with exposure. Initial employment date could be of some importance since many of the workers hired during the first few years of the establishment of the Hanford plant were recruited from munitions plants. There is no strong relationship of date of employment and level of exposure except that early terminees have little exposure.

3. Methods of analysis. The analysis of this data set presents a number of challenging problems. The time dependent (cumulative) nature of the exposure data in combination with special problems involving the study of a working population create potential sources of bias. In view of the considerable variability in the distribution of exposure among workers, methods of analysis which relate death rates directly to exposure are probably less subject to bias and more powerful against alternatives of positive radiation effects than methods based on comparison of the entire study population with an external control.

The method which has been chosen to analyze this data is to compare the doses of those workers dying from a particular cause to the doses of comparable workers at risk of dying at the same time. For example, the dose of a worker dying in 1967 at age 56 can be compared with the doses of persons alive and at risk of dying at the beginning of 1967 and aged 55-59 at this time. Only exposure accumulated up to 1967 can be appropriately included for the comparison group even though many of its members accumulate additional exposure in the years that follow. Variables other than age can be considered in defining the risk set and

other functions of exposure could be considered. Exposures can be lagged for various intervals. That is, we might consider only exposure accumulated five years prior to death, or as of 1962 in the above example.

This approach can be described in terms of the proportional hazards model in which the incidence rate or hazard at time t is given by

$$\lambda(t; z, \underline{x}) = \lambda_0(t; \underline{x}) \exp(\beta z)$$

where t denotes time (in one year intervals), $\underline{x}$ denotes the various stratification variables, and z denotes cumulative exposure at time t . This model was originally proposed by Cox [6] and is described in this volume by Prentice [19].

The derivative with respect to β of the log likelihood function can be shown to be

$$L'(\beta) = \sum_{i=1}^n z_i(t_i) - \frac{\sum_{\ell \in R_i} z_{\ell}(t_i) \exp[\beta z_{\ell}(t_i)]}{\sum_{\ell \in R_i} \exp[\beta z_{\ell}(t_i)]}$$

where i indexes the deaths due to a particular cause, t_i is the time (calendar year) of death for worker i , $\underline{x}_i$ denotes the stratum for worker i at time t_i , $R_i = R(t_i, \underline{x}_i)$ denotes the risk set of workers in stratum

$\underline{x}_i$ alive at time t_i , $z_{\ell}(t_i) = \sum_{j=I_{\ell}}^{t_i-G-1} d_{\ell j}$, $d_{\ell j}$ is the annual recorded

exposure for worker ℓ in year j , I_{ℓ} is the year of initial employment for worker ℓ , and G is a designated lag time. Cox notes that a test for $\beta = 0$ can be based on

$$L'(0) = \sum_{i=1}^n [z_i(t_i) - \mu_i]$$

$$\mu_i = \frac{\sum_{\ell \in R_i} z_{\ell}(t_i)}{N_i}$$

where

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and $N_i = N(t_i, x_i)$ is the number of workers in risk set i . The test can be regarded as a permutation test of

$$Z = \sum_{i=1}^n z_i(t_i)$$

conditional on the risk sets R_i . Asymptotically, Z will be normal with mean

$$\mu = \sum_{i=1}^n \mu_i$$

and variance

$$\sum_{i=1}^n \sigma_i^2$$

$$\text{where } \sigma_i^2 = \frac{\sum_{\ell \in R_i} [z_\ell(t_i) - \mu_i]^2}{N_i}$$

Evaluating the null distribution of $L'(0)$ is difficult in view of the extremely skewed data. For very rare causes of death, an exact permutation test may be feasible, or Monte Carlo simulation might be considered. Grouping doses makes a permutation test somewhat easier but results in some loss of information. Transforming the data is still another solution, but may not be completely acceptable since transformations have not been routinely used in other human studies of radiation effects. The solution we have settled upon is to adjust a normal approximation by using the 3rd and 4th null moments of Z . This method makes use of an Edgeworth series and is described in Cramer [7].*

For the analysis presented in this paper, deaths occurring over the period January 1, 1955 through March 31, 1974 are grouped into one-year intervals. Stratification variables (x) are age (in five-year intervals), occupation (craftsmen-operators and other workers), length of employment (less than 10 years and 10 or more years), initial employment

*This method was suggested for use with this data by Charles Land.

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date (before 1950 and 1950 and after), and employment status (employed and terminated). Several of these variables are time dependent so that workers will move from one stratum to another as they are followed forward in time.

A worker who develops terminal cancer while employed may terminate employment a few months before his death occurs. Because this worker should properly be compared with others in the employed stratum, workers were considered to be employed until two years after the last date for which dosimetry data were available. A lag of two years ($G=2$) was also introduced in defining the cumulative doses and in calculating length of employment.

The method is illustrated for myeloid leukemia. There were five deaths from this cause in the study population with total exposure (Z) of 13.18 rem. The total of the means from the five risk sets was 13.83 rem with a total variance of 111.71. Evaluating the statistic

$$y = \frac{Z - \sum_{i=1}^n \mu_i}{\left[\sum_{i=1}^n \sigma_i^2 \right]^{1/2}}$$

we obtain $-.06$ and clearly this population exhibits no evidence of radiation induced myeloid leukemia at this time. In general, the statistical significance can be evaluated by considering a normal approximation for y with adjustment using higher order moments of the risk sets.

4. Point estimates of effects. Since there is no evidence of a correlation of radiation exposure with death from myeloid leukemia in this population, and since this result is compatible with effect estimates obtained in other studies of radiation exposure, these data do not warrant modifying point estimates obtained from these other studies. The same observation applies to the consideration of most other specific cancer types. The analysis described above has been applied to all

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causes of death, all malignant neoplasms, and several specific cancer types with the results summarized in Table 1. For most causes there is no evidence of a positive association with radiation exposure.

TABLE 1. Results of analysis. (See text for complete description.)

Cause of Death	Number of Deaths (n)	Observed Mean ($\bar{z}/n$)	Expected Mean ($\bar{e}/n$)	Normal Deviate (y)	Adjusted p-value (one-tailed)
All Causes	1782	2.09	2.25	-1.51	0.94
All Malignant Neoplasms (M.N.) (140-209)	363	2.22	2.33	-0.46	0.67
M.N. of Buccal Cavity (140-149)	15	1.20	2.37	-0.93	0.81
M.N. of Stomach (151)	20	0.79	1.56	-1.09	0.87
M.N. of Colon (153)	39	1.81	1.79	0.02	0.45
M.N. of Pancreas (157)	25	4.29	2.58	1.86	0.045
M.N. of Other Digestive Organs (150, 152, 155-156)	27	0.78	1.60	-1.31	0.92
M.N. of Lung (162)	106	2.76	2.94	-0.36	0.63
M.N. of Prostate (185)	22	0.89	2.58	-1.61	0.97
M.N. of Brain (191-192)	16	2.52	2.32	0.19	0.37
Lymphosarcoma and Reticulum Cell Sarcoma (200)	11	1.28	1.78	-0.46	0.61
Hodgkin's Disease (201)	5	1.80	1.89	-0.07	0.44
Myeloid Leukemia (205)	5	2.64	2.77	-0.06	0.42
Other Leukemia (204, 206-207)	5	0.23	0.79	-1.06	0.94
Multiple Myeloma (203)	6	13.73	3.36	4.20	0.0008
Other Neoplasms of Lymphatic and Hematopoietic Tissues (202, 208-209)	5	0.21	1.28	-0.92	0.72
All Other Cancers	56	1.80	2.18	-0.68	0.73
All Non-Cancer Causes	1419	2.06	2.23	-1.46	0.93

There are two specific cancer types which exhibit significant positive correlations with radiation exposure - multiple myeloma and cancer of the pancreas. Both inferences are based on a small number of deaths with high exposures. For example, the inference for multiple myeloma results from three deaths with high exposures of 20.0, 27.0 and 34.4 rem compared with the respective expected values of 4.3, 7.2 and 4.3 rem. For cancer of the pancreas, the difference between observed and expected totals results almost entirely from four deaths with exposures of 10.8, 16.9, 26.9, and 28.3 rem compared with the respective expected doses of 2.1, 6.2, 7.1 and 7.2 rem. The possibility that other factors, such as occupational exposure to other agents at Hanford or elsewhere, are the underlying causes of one or both of the correlations cannot be ruled out.

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There is evidence from other studies [5,15] that multiple myeloma and cancer of the pancreas have been induced by radiation, but it is not nearly as substantial as that for a number of other cancer types, the most notable being myeloid leukemia.

Meaningful estimates of risk for multiple myeloma and cancer of the pancreas are not likely to be achieved from this data given the small number of deaths involved and the lack of knowledge concerning such factors as the shape of the dose-response curve, the relationship of the effect to the timing of the exposures, and whether an additive or multiplicative model is appropriate. Even if effects involving larger number of deaths are eventually identified, this data will probably not be adequate to distinguish among various models.

If one wishes to postulate a model, the likelihood equations can of course be specified. If Cox's proportional hazards model is chosen, an approximate solution can be obtained fairly easily by expanding $L'(\beta)$ in a Taylor series about zero to obtain

$$L'(\beta) = \sum_i z_i - \left[(\kappa_{1i} + \beta \kappa_{2i} + \frac{\beta^2}{2} \kappa_{3i} + \frac{\beta^3}{6} \kappa_{4i} + \dots) \right]$$

where κ_{ki} is the k th cumulant of the risk set R_i . Since an r th order expansion of $L'(\beta)$ is a function of Z and the first $r+1$ moments of the risk sets R_i , only one pass through the complete data set is required for all causes of death of interest.

The proportional hazards model of Cox is a relative or multiplicative model in that the risk from radiation exposure is assumed to be proportional to the risk from other carcinogens ("spontaneous" risk). This assumption is supported by several studies of radiation effects summarized in this volume by Smith [20]. An alternative model which is useful from the standpoint of radiation protection is the absolute or additive model in which the risk from radiation exposure is assumed to be constant for all segments of the population. The needed likelihood equations for the absolute model can be derived but since the hazard

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for the absolute model is of the form $\lambda(t; \underline{x}) + f(z)$, the spontaneous rates $\lambda(t; \underline{x})$ will not "cancel out." With a large number of time periods and strata, the $\lambda(t; \underline{x})$ cannot be efficiently estimated from the data so that an external control population would be required.

5. Upper confidence limits on effects. For cancer types for which these data provide little or no evidence of effect, an upper bound or confidence limit is of interest. Since current estimates are based on linear models, the two models considered for this purpose are the relative linear model

$$\lambda(t; z, \underline{x}) = \lambda(t; \underline{x})[1 + \beta z]$$

and the absolute linear model

$$\lambda(t; z, \underline{x}) = \lambda(t; \underline{x}) + \beta z.$$

The relative model above can be considered a modification of Cox's model with $\exp(\beta z)$ replaced by $1 + \beta z$.

The determination of confidence limits requires testing hypotheses of the form $\beta = \beta_0$ where β_0 is some very large effect, perhaps 10 or even 100 times the BEIR estimates. Methods which rely completely on the data for estimates of spontaneous risks (such estimates are implicit in the use of Cox's model) present problems. The difficulty is that given the number of deaths that have occurred, very large effects can be present only if a high proportion of these deaths are radiation induced resulting in estimates of spontaneous risks which are far too low to be credible. By introducing rates from an external population, this difficulty can be averted.

A simple approach to this problem is to compare the number of deaths observed to the number expected for a given β . The expected deaths will be given by

$$\sum_{t, \underline{x}} N(t; \underline{x}) \lambda(t; \underline{x}) [1 + \beta \mu(t; \underline{x})]$$

for the relative linear model and by

$$\sum_{t, \underline{x}} N(t; \underline{x}) [\lambda(t; \underline{x}) + \beta_A \mu(t; \underline{x})]$$

for the absolute linear model.

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A more powerful test of significance can be obtained by evaluating the distribution of Z for a specified β . The mean, variance and higher order moments of Z (conditional on the risk sets) can be derived by considering Z as the sum over all person-years at risk of the variables $z_l(t) \delta_l(t)$ where $\delta_l(t) = 1$ if death occurs for worker l at time t , $\delta_l(t) = 0$ otherwise. For the relative linear model,

$$\begin{aligned} E(Z) &= \sum_{\tilde{t}\tilde{x}} \sum_{l \in R(\tilde{t};\tilde{x})} z_l(t) E[\delta_l(t)] \\ &= \sum_{\tilde{t}\tilde{x}} N(\tilde{t};\tilde{x}) \lambda(\tilde{t};\tilde{x}) [\mu(\tilde{t};\tilde{x}) + \beta \mu^{(2)'}(\tilde{t};\tilde{x})] \end{aligned}$$

where

$$\mu^{(k)'}(\tilde{t};\tilde{x}) = \frac{\sum_{l \in R(\tilde{t};\tilde{x})} z_l^k(t)}{N(\tilde{t};\tilde{x})}$$

and $\text{Var}(Z)$ is approximately equal to

$$\begin{aligned} &\sum_{\tilde{t}\tilde{x}} \sum_{l \in R(\tilde{t};\tilde{x})} z_l^2(t) E[\delta_l(t)] \\ &= \sum_{\tilde{t}\tilde{x}} N(\tilde{t};\tilde{x}) \lambda(\tilde{t};\tilde{x}) [\mu^{(2)'}(\tilde{t};\tilde{x}) + \beta \mu^{(3)'}(\tilde{t};\tilde{x})] . \end{aligned}$$

Higher order moments can also be derived, and analogous expressions will hold for the absolute model.

If the number of deaths from a particular cause is less than the number expected assuming no radiation effect, given by $\sum_{\tilde{t}\tilde{x}} N(\tilde{t};\tilde{x}) \lambda(\tilde{t};\tilde{x})$, one may wish to adjust the spontaneous rates by multiplying by the ratio of observed and expected deaths, commonly known as the standardized mortality ratio. The resulting rates have been shown by Breslow [2] to be maximum likelihood estimates under the multiplicative model (if $\beta=0$). This adjustment, which can be regarded as conservative in the sense that hypotheses of large effects are less likely to be rejected with the smaller values of spontaneous rates, could be carried out separately for

strata defined by variables for which there is no comparable breakdown for the control population.

6. Future analysis. The application of the techniques discussed in this paper will include analyzing this data with various transformations and with various lag periods. Since measurement error for large exposures is undoubtedly greater than for smaller exposures, a square root or logarithmic transformation may be desirable. Although at this time it is unlikely that we can learn much about time to response distributions from these data, findings for most cancer types are more credible if they hold up when exposures are lagged for 10 or 15 years. Other options for treating the exposure data include weighted functions of the annual exposures similar, for example, to that considered by Lundin [11]. Such functions could be specified in accordance with a variety of theories concerning the dose response relationships.

As an alternative to stratification, additional independent variables might be introduced in the proportional hazards model. There may be practical difficulties in carrying out the necessary computations for many causes of death on this large data set, but such refinements might be considered for a few cancer types of special interest, possibly using the case-control approach of Breslow [3]. Another application of the proportional hazards model worth considering for this data set, also proposed by Breslow [2], allows for the introduction of rates from an external population as a method of refining control of age and calendar year.

It is important that analysis of these data be updated as additional mortality data become available and that analysis be undertaken of similar data sets. It must however be recognized that because of the relatively small exposures received by such occupational groups, the potential of these data for increasing our understanding of dose-response relationships is distinctly limited.

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